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«Secrets» of heart transplantation

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Unfortunately, there really are no «secrets» as such. The right ventricle's contribution to clinical medicine has been largely neglected until recently. Donor management, recipient preparation, and the anatomic and physiologic characteristics of the right ventricle are concepts that we find helpful in the perioperative management of heart transplant recipients.

Donor management. It is truly unfortunate that caring for the donor is often relegated to the most junior members of the anesthesia team. The attitude of: «He's already dead, what else can go wrong?» misses opportunities to improve recipient outcome.

Brain death frequently causes profound changes in sympathetic outflow and endocrine function. Experimental and clinical observations [1] of «sympathetic storm» haracterized by radically elevated catecholamine levels and marked hypertension is thought to precipitate ischemia and microvascular changes in the donor organs. This is often followed by hypotension which may be due to catacholamine depletion often requires aggressive treatment with exogenous catecholamines to stabilize the hemodynamics of the donor. The once widely held view that patients requiring significant catecholamine support are not suitable candidates for donation is being questioned [2].

The inflammatory cascade is also initiated [3]. Thyroid hormone levels (both T4 and T3) decrease, as do cortisol and antidiuretic hormone. Decreased responsiveness to normal circulating levels of thyroid hormones is termed «sick euthyroid syndrome» and is common in this setting. A «cocktail» of T3 (4 mcg bolus followed by 3 mcg/hr), desmopressin (or vasopressin), and methylprednisolone (15 mg/kg/day) is commonly employed and has allowed successful transplantation of organs previously deemed unsuitable [4].

Recipient preparation. Optimizing the recipients' overall status prior to transplantation is thought by many to improve outcome [5]. Although definitive data is lacking outcomes appear to be improved if the transpulmonary gradient can be reduced to less than 15 mmHg, the pulmonary vascular resistance to less than 4 Wood units, and the systolic pressure less than 50 mmHg. Therefore, patients with preoperative pulmonary hypertension should undergo provocative testing with pulmonary vasodilators to assess its reversibility. Often, aggressive therapy will lower the pulmonary artery pressures to levels acceptable for transplantation. Although outcomes are improved, they do not equal those of patients presenting for transplantation without pulmonary hypertension. Patients awaiting transplantation are frequently invasively monitored and treated with parenteral drugs to improve cardiac output and decrease pulmonary vascular resistance (PVR). Prevention of renal failure (cardio-renal syndrome) and deterioration of liver function are important, but not always easy to achieve in the face of low cardiac output and high right-sided pressures. «Renal dose» dopamine has little evidence to support it, but retains many advocates. Fenoldopam and nesiritide have both been tried to promote diuresis and preserve renal function with varying results.

As discussed below, decreasing pulmonary artery pressure (PAP) is key to preventing and treating right ventricular failure in the donor heart. While it is unlikely that PAP will normalize in patients with deteriorated chronic heart failure, any improvement is beneficial. The more acute the onset of heart failure, the more improvement might be expected. Nitric oxide (NO), prostaglandins,

milrinone (PDE3 inhibitor), nitroglycerine, and sildenafil (PDE5 inhibitor) all have their advocates. While some are easier to use (e.g. NO does not affect the SVR but is very expensive) the specific drugs are not as important as an aggressive pharmacologic attempt to decrease PAP. In this context, sildenafil is usually well tolerated and has been shown to be synergistic with both NO and prostaglandins [6].

The Right Ventricle. Right heart dysfunction is so common after heart transplantation that Saleh [7] describes it as «universal». It accounts for 50% of acute perioperative complications and 19% of acute deaths.

Anatomy. Until relatively recently, the RV was treated somewhat as a second-class citizen with little appreciation for its potential for good or ill. Indeed, the fact that patients survived to adulthood following a Fontan procedure was cited as evidence that the RV was virtually expendable.

The RV free wall is composed of transversely oriented fibers. The only oblique fibers are located in the septum and are usually considered part of the left ventricle [7]. The ventricle acts mechanically like a bellows with the free wall contracting against the septum. There is no «wringing» motion as is seen in the LV. This configuration is ill suited to increases in afterload. However, the steep ventricular function curve of the RV predicts that it will be quite sensitive to afterload reduction, which is what is observed clinically and experimentally [8].

The thin walled RV is normally perfused in both systole and diastole since RV systolic pressure is usually less than aortic diastolic pressure. However, as RV pressure rises coronary perfusion falls leading to RV oxygen supply-demand imbalance, ischemia and decreased RV contractility. A vicious downward spiral of ischemia, decreased contractility, and decreased coronary perfusion is thus initiated as demonstrated by Guyton [9].

Physiology. Decreased contractility alone rarely causes RV failure if the PVR is normal. Since PVR is normally about 10% of SVR, significant pressure is not required to transport blood through the lungs. Under normal conditions, the RV stroke work is about 25% of the left ventricular stroke work. Total occlusion of RCA or replacement of most of the free RV wall with synthetic material does not cause RV failure if the PVR is normal [9] and the RV isn't dilated [10].

As PVR rises, contractility increases by homeometric autoregulation (Anrep effect, probably mediated through calcium), then by endogenous release of catechols. When this compensatory mechanism is overwhelmed, the RV dilates. Dilation shifts the intraventricular septum toward the LV. This change in geometric conformation decreases the efficiency of the bellow-like RV contraction and RV stroke volume decreases [11–13]. Since both ventricles share a common pericardial space, the dilated RV compresses the LV decreasing its preload and therefore its stroke volume [14]. This is also seen in postoperative patients, albeit to a lesser degree since the pericardium is usually left open.

Therapy is directed at improving RV function by decreasing RV afterload with pulmonary vasodilators and restoring systemic blood pressure by increasing the SVR with vasopressors. Increasing systemic blood pressure improves RV perfusion [15], and the increased afterload's effect on the LV can shift the septum back toward the RV. This can improve the RV's ability to contract efficiently. Interestingly, this septal shift can also be accomplished experimentally by incremental banding of the aorta to increase afterload on the left ventricle.

As with the LV, appropriate rhythm and timing of atrial contraction become increasingly important as function deteriorates. Supraventricular tachyarrhythmias are not well tolerated. Biventricular pacing can significantly improve cardiac output by improving LV-RV coordination.

Mechanical Circulatory Support. Medical therapy alone is frequently insufficient to overcome acute RV failure. Support with mechanical circulatory devices (MCS) has allowed salvage of a significant number of these patients without resorting to retransplantation. Often MCS can support the patient to allow time for the acute insults associated with transplantation (e.g. preexisting pulmonary hypertension, PH induced by CPB or transfusion, or RV depression from suboptimal preservation or long ischemic times) to resolve or at least improve. Generally, devices designed for left ventricular support are adapted to the RV. In borderline cases, intra aortic balloon counterpulsation is often attempted but usually is insufficient. Extracorporeal membrane oxygenation can be inserted without the need for resternotomy. Centers reporting good success with MCS seem to opt for it early in the post transplant period [16, 17].

Pulmonary Vasodilators. Until the introduction of nitric oxide attempts at decreasing PVR were often limited by systemic hypotension. While the response to NO is not universal, NO is easy to administer and monitor (we even administer it through nasal cannulas in extubated patients). Rebound upon discontinuation can usually be prevented or managed with oral sildenafil or inhaled agents.

Inhaled prostacyclin is efficacious and cost effective. However the glycerine vehicle can foul ventilator valves and continuous administration is necessary. Iloprost is an aqueous derivative that can be administered every 2–3 hours. Both are synergistic with sildenafil.

Nitroglycerine, nitroprusside and milrinone have all been given by inhalation, but are considered experimental at this time. When given by inhalation, they have little effect on the SVR and do not increase intrapulmonary shunting as they do when given intravenously. Acidosis increases PVR as does hypothermia and both should be avoided.

Inotropic Support. Supporting the SVR with alpha agonists can increase the PVR as well, although not to the same extent due to the higher distribution of receptors in the systemic circulation. In this context, vasopressin is thought to increase PVR less than an equivalent dose of alpha

agent. This is probably due to fewer vasopressin receptors being present in the pulmonary circulation relative to the systemic circulation. When used in low doses (1–4 mcg/hr) organ ischemia is not usually a problem.

Contractility can be supported with beta agonists and/or phosphodiesterase inhibitors, the combination of which seem to act synergistically. Dobutamine and epinephrine have both been used with success. Isoproterenol often shunned for its potential to cause tachycardia and hypotension is an excellent beta agonist, chronotrope, and pulmonary vasodilator and we have found it useful in this context.

Surgical Technique. Bicaval anastomosis is the preferred method at this time, providing less interference with sinus rhythm and less tricuspid regurgitation than atrial anastomosis. Although short-term benefits have been demonstrated [18] long-term improvements are less convincingly demonstrated.

Minimizing time on cardiopulmonary bypass is desirable as pulmonary endothelium derived relaxant factors (including nitric oxide) are decreased with duration of bypass. Minimizing the use of blood products similarly improves RV function by minimizing the increase in PVR associated with their use. Nitric oxide, in addition to its vasodilating properties prevents margination of leukocytes and platelets with favorable effects on inflammation and pulmonary hypertension [19].

Atrial septostomy (percutaneous or surgical) have been tried in an effort to create a «pop-off» for the RV. Most of these reports are in the pediatric pulmonary hypertension literature, and the results have been disappointing.

Following separation from cardiopulmonary bypass, the transesophageal echocardiogram should be evaluated. Tricuspid regurgitation and the anastomoses between the cavae and right atrium evaluated for stenosis. The left atrial anastomosis is usually seen as a large ridge in the left atrium. RV outflow tract obstruction due to kinking of the PA is easily visualized, although rare. Wall motion abnormalities and RV function should be evaluated to help determine the need for inotropic support.

Postoperative Ventilatory Management. Extremes of lung volume increase PVR. At the low end, the microvasculature is compressed by the interstitial tissue and at the high end, by the overdistended alveoli. PVR is lowest at residual volume. These conditions are met through the use of a «protective» ventilatory strategy, sometimes referred to as «open lung» ventilation. Tidal volumes of 6–8 cc/kg of ideal body weight and sufficient PEEP to prevent cyclical collapse and reopening of alveoli achieve these goals. If CO2 elimination is a problem, heavy sedation and muscle relaxation will allow the patient to better tolerate the higher respiratory rates needed.

Emergence from anesthesia or sedation in the ICU can be associated with marked increases in PAP due to the increased sympathetic outflow it causes. Indeed, we have seen acute right heart failure develop in a previously normally functioning heart when weaning from ventilation was attempted. In this context, we have found dexmedetomidine to be very helpful in weaning these patients for its sedative and sympatholytic/anxiolytic effects. Combining it with judicious use of narcotics can generally control this problem.

While there are, regrettably, no secrets to successful heart transplantation, attention to the details of RV physiology and use of newer drug therapies can improve outcome.

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